



## **UNITED STATES AIR FORCE RESEARCH LABORATORY**

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### **SHORT-TERM FATIGUE MANAGEMENT: A CROSS-STUDY ANALYSIS OF THE EFFECTS OF DEXTROAMPHETAMINE AND MODAFINIL IN SLEEP-DEPRIVED AVIATORS**

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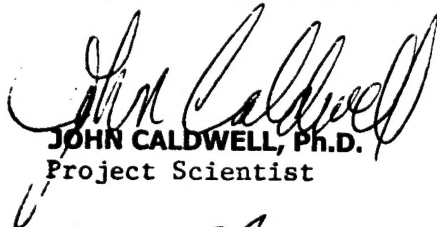
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Fatigue has been identified as an important operational problem in both military and civilian aviation (Caldwell, 1997; Rosekind et al., 2000). Requirements for extended duty periods, inconsistent work/rest schedules, multiple-time-zone operations, and night flights combine to potentially degrade performance and alertness in the cockpit. Duty-time limitations traditionally have been relied upon to manage aircrew fatigue; but problems persist as evidenced by the fact that significant fatigue-related mishaps continue to occur. Because of this, it may be worthwhile to consider the limited use of alternative strategies such as stimulants. The data from five placebo-controlled studies (four with dextroamphetamine and one with modafinil) were combined to examine the overall efficacy of stimulants for preserving flight performance, physiological alertness, and subjective vigilance in sleep-deprived pilots. Statistically-significant ( $p < .05$ ) drug main effects and drug-by-time interactions revealed that both compounds maintained flight performance across six maneuvers, attenuated deprivation-related increases in slow-wave electroencephalogram (EEG) activity, and preserved subjective ratings of psychological vigor throughout 34-39 hours of continuous wakefulness, whereas substantial difficulties were observed under placebo. Furthermore, the drug-related effects were remarkably consistent across all of the five studies that were examined. Dextroamphetamine and modafinil are effective for sustaining aviator alertness and performance (although, some potentially dose-related adverse effects were observed with modafinil). While it may be ill-advised to rely upon the long-term use of these or other pharmacological strategies as the sole remedy for fatigue in aviation, stimulants can be counted upon to temporarily mitigate the deleterious effects of fatigue during operations in which no other countermeasures are feasible.

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## INTRODUCTION

Pilot fatigue is an operational problem throughout aviation, but especially in operations involving sleep loss from circadian disruptions, increased sleep pressure from extended duty, and impaired arousal associated with night duty (Akerstedt, 1995). Aviator fatigue is associated with degradations in response accuracy and speed, the unconscious acceptance of lower standards of performance, impairments in the capacity to integrate information, and narrowing of attention that can lead to forgetting or ignoring important aspects of flight tasks (Perry, 1974). Fatigued pilots tend to decrease their physical activity, withdraw from social interactions, and lose the ability to effectively divide mental resources among different tasks. As sleepiness levels increase, performance becomes less consistent and vigilance deteriorates (Dinges, 1990). Even the most basic types of psychomotor performance are degraded by sleepiness/fatigue. Dawson and Reid (1997) report that only 17 hours of sustained wakefulness can produce psychomotor deficits equivalent to those observed with a blood alcohol concentration (BAC) of 0.05 percent while 24 hours of sustained wakefulness is associated with decrements equivalent to those observed with a BAC of 0.10 percent. Thus, it is clear that fatigue is a threat to flight safety.

### The Contribution of Fatigue to Mishaps

Sixty-five percent of air accidents have been attributed to human error since the start of the jet age, but the percentage attributable to sleep loss/fatigue remains uncertain (Lauber and Kayten, 1988). A National Transportation Safety Board (NTSB) study of major accidents in domestic air carriers from 1978 through 1990 in part concluded that "... Crews comprising captains and first officers whose time since awakening was above the median for their crew

position made more errors overall, and significantly more procedural and tactical decision errors” (NTSB, 1994, p. 75). Kirsh (1996) estimates that fatigue may be involved in 4-7% of civil aviation mishaps, and data from the U.S. Army suggest fatigue is involved in 4% of Army accidents (Caldwell and Gilreath, 2002). Furthermore, 25% of the Air Force’s night tactical fighter Class A accidents were attributed to fatigue between 1974 and 1992, and 12.2% of the Navy’s total Class A mishaps were thought to be the result of aircrew fatigue from 1977 to 1990 (Ramsey and McGlohn, 1997). At first glance, some of these percentages appear rather inconsequential; however, it should be noted that the cost of a single major civil aviation accident can exceed \$500 million in total financial losses, while the costs in terms of personal suffering are often inestimable (Lauber and Kayten, 1988). In addition, the impact of a catastrophic mishap on the revenues of an airline is probably severe. Although no concrete figures are available, it is likely that substantial public-relations “fallout” resulted from events such as the crash of Korean Air flight 801 in which 228 people died (NTSB, 1999); the near crash of China Airlines flight 006 in which two people were severely injured and other passengers were traumatized (Kolstad, 1989); or the accident involving American Airlines 1420 in which 11 people died (Krause, 1999). In each of these cases, crew fatigue from long duty periods and/or circadian factors have been implicated.

#### Extended Work and Wakefulness Periods are Common in Aviation

Extended duty times (work shifts that exceed 8 hours) are common in both civilian and military aviation. In civil aviation, Gander et al. (1998a) found that one sample of pilots involved in short-haul trips worked an average of 10.6 hours per day, while another sample of long-haul pilots worked an average of 9.8 hours per day (Gander et al., 1998b). Rosekind

et al. (1994) found that a sample of long-haul pilots worked from 8.4 to 14.8 hours per day. No doubt, many of these pilots were continuously awake for several more hours beyond the 11-15 hours logged as "duty time" considering that commute times and other nonwork activities are not logged as "duty." Gander et al. (1998b) found that the average period of wakefulness for her subjects was in excess of 20 hours per duty day. In military aviation, the problem may be more severe, particularly during combat operations where the duty days are lengthy and there are few days off between duty cycles. The U.S. Army Field Manual (FM) 22-9 (Department of the Army, 1991) advises that "Soldiers [and aviators] in continuous operations can expect to be deprived of extended regular sleep, *possibly any sleep*, for as long as three to five days" (p 3-10). In a survey of U.S. Air Force pilots deployed in the Gulf War, Emonson and Vanderbeek (1995) found that 81 percent of one group of pilots reported working more than 12 hours per day, and 49 percent reported routinely working more than 14 hours per day.

### The Effects of Extended Duty

The effects of extended work schedules are not fully understood, but prolonged work shifts (greater than 8 hours) have been associated with decrements in alertness and performance (Rosa and Bonnet, 1993). Morisseau and Persensky (1994) found that overtime in the nuclear industry was related to an increase in incidents, and Hamelin (1987) demonstrated a relationship between longer work hours and an increased risk of truck accidents, particularly at night. More to the point, Samel, Wegmann, and Vejvoda (1997) have shown that pilot fatigue increases progressively as a function of flight length, and



Rosekind et al. (1994) revealed that some pilots experience increased performance lapses during the latter portion of long-haul flights.

### Night Flights are More Susceptible to the Impact of Fatigue than Day Flights

Nontraditional work hours contribute substantially to the risk of fatigue-related problems throughout society (Dinges, 1995), and there is evidence that a number of high-profile catastrophies (i.e., the grounding of the Exxon Valdez, the space shuttle Challenger accident, the crash of Korean Air flight 801, and the near meltdown at Three Mile Island) were at least partially attributable to fatigue associated with night work (Mitler et al., 1988; NTSB, 1990; NTSB, 1999). Studies focused on aviation operations reveal that long-haul night flights are especially vulnerable to cognitive lapses or “microsleeps”—brief periods during which sleep uncontrollably intrudes into wakefulness. Moore-Ede (1993) found a tenfold increase in lapses accompanied by a significant worsening of performance errors between the hours of 0400 and 0600. Klein, Bruner, and Holtman (1970) reported that pilots’ abilities to fly a simulator at night decreased to a level comparable to that observed with a BAC of 0.05%. Wright and McGown (2001) found that while sleepiness of long-haul pilots increased during both daytime and overnight flights, the occurrence of sleep was more frequent on flights that departed late in the night compared to those that departed earlier. Rosekind et al. (1994) found a substantial increase in slow-wave EEG activity and/or slow eye movements (indicating severe fatigue) during long flights--especially those occurring at night.

## Several Factors Combine to Produce Fatigue in Aviation Personnel

Aircrews are susceptible to fatigue stemming from all of the factors discussed above, but extended duty periods (with extended periods of wakefulness) and the requirement to work on nonstandard schedules are particularly problematic. In addition, circadian disruptions from traveling across time zones, and sleep restrictions associated with short crew-rest periods (combined with sleep opportunities that are out of phase with normal body rhythms) can impair alertness and performance (Gander et al., 1998b). Working under these conditions in cockpits that are highly automated and sometimes cramped, poorly ventilated, noisy, and dimly lit, can make pilots uniquely susceptible to fatigue (Battelle, 1998). The situation is further complicated by the fact that flight schedules (and crew duty cycles) are unpredictable due to inclement weather and mechanical difficulties. Furthermore, efficacious fatigue countermeasures such as cockpit naps (Rosekind et al., 1994) often cannot be successfully implemented either because of regulatory or operational constraints.

## A Possible Role for Stimulant Compounds

In situations where prolonged work hours are required despite inadequate sleep and circadian disruptions, stimulants may be a suitable short-term remedy for the effects of severe fatigue. Stimulants are effective and easy to use, and their feasibility is not dependent upon environmental manipulations or scheduling modifications. This explains why amphetamines have been used extensively by various military forces during periods of conflict, and why there is such great interest in the new alertness-promoting substance modafinil.

The efficacy of dextroamphetamine (Dexedrine®) has been well-established in sleep-deprived personnel in field settings (Senechal, 1988; Cornum, 1992; Emonson and Vanderbeek, 1995), and in a series of laboratory-based aviation studies (Caldwell et al., 1995; Caldwell, Caldwell and Crowley, 1997; Caldwell and Caldwell, 1997; Caldwell, et al., 2000a). However, because amphetamine abuse can produce some problems, modafinil is being considered as a possible alternative (Lyons and French, 1991). Unfortunately, actual “real-world” performance studies on modafinil are scarce, and to date, this compound has not been adequately tested in field situations (Akerstedt and Ficca, 1997). However, a laboratory study by Pigeau et al. (1995) suggests that 300 mg of modafinil equates to 20 mg of dextroamphetamine at least in terms of maintaining mood and cognitive performance, and Caldwell et al., (2000b) found that repeated 200-mg doses of modafinil were effective for sustaining the performance of pilots exposed to 40 hours of sleep deprivation (although some side effects were noted).

The results of these studies suggest that there may be a role for dextroamphetamine and modafinil in select aviation operations. These compounds have noteworthy alertness-enhancing properties that could enhance the safety of aircrews under situations in which extreme operational fatigue is simply unavoidable. To illustrate this point, the data from several studies in which sleep-deprived helicopter pilots were tested under either dextroamphetamine or modafinil were combined and analyzed in a single unified effort. These studies, conducted at the U.S. Army Aeromedical Research Laboratory, include three evaluations of Dexedrine® and one evaluation of modafinil throughout 40 hours of continuous wakefulness. In addition, one study of Dexedrine® in which pilots were tested throughout 64 hours sleep loss was included. Three of the 40-hour studies (two Dexedrine

and one modafinil) were conducted in a UH-60 helicopter flight simulator, and one 40-hour study (with Dexedrine) was completed in an actual UH-60 aircraft. The 64-hour study was performed in the simulator. Objective measures of flight performance, quantitative electroencephalographic data, and subjective mood ratings from each study were examined.

## METHODS

The five investigations were conducted under virtually identical research protocols. Thus, all of the flights were conducted at the same times across all studies, and the other tests were given at nearly the same times (the scheduled times for mood and electroencephalographic data collection did not differ more than 20 minutes from one protocol to the other). Since one of the studies (the 64-hour protocol) involved additional data collection that extended beyond the period assessed in the 40-hour protocols, the final 24 hours were dropped from the present statistical analysis.

### Participants

Thirty-four participants were tested. All were current and qualified UH-60 helicopter pilots. The mean age of the sample was 31 years (ranging from 24-46 years of age), and the mean amount of flight experience was 1,238 hours (ranging from 140-5,500). Of the 34 volunteers who were evaluated, 7 were female (the overall makeup of the population of Army aviators is approximately 3 percent female). All volunteers passed a medical prescreen (to rule out significant illnesses of any type, sleep difficulties, allergic reactions to medications, etc.) prior to admission into the protocols. Participants signed consent forms which fully disclosed any hazards associated with the experiments. The research protocols

were reviewed by the Laboratory's Human Use Committee and The Surgeon General of the Army's Human Subjects Research Review Board prior to execution. The participants were treated in accordance with the "Ethical Principles of Psychologists and Code of Conduct" (American Psychological Association, 1992).

Participants were not permitted to ingest caffeinated products at any time during the protocols, and caffeine users were advised to refrain from ingesting caffeine at least 2 days prior to participation. The majority of the subjects were not heavy caffeine users; however, several did experience headaches which were thought to be associated with caffeine withdrawal at the outset of some of the protocols. Fortunately, these appeared to be equally distributed among those who received the stimulant first and those who received placebo first.

### Materials

Dose Preparation. In the dextroamphetamine studies, two orange gelatin capsules were administered at each dose time (midnight, 0400, and 0800) with 8 oz. of orange juice. Each active capsule contained one 5-mg tablet of Dexedrine (two were given per dose), and each placebo capsule contained lactose powder. In the modafinil study, two 100-mg white tablets were administered at each dose time (2300, 0300, and 0700--modafinil takes longer to achieve peak plasma concentration than Dexedrine). The active tablets matched the placebo tablets in appearance. Each dose was given with a glass of water. Dosage levels were not adjusted according to body weights since this would not be done in the operational setting.

UH-60 Simulator. Simulator flights (performed in four of the five studies) were conducted in a specially-instrumented UH-60 simulator (CAE-Link Corporation, Model Trainer ASSY-2B38, Binghamton, NY) with computer-generated visuals (set for standard

daytime flight), a six-degree-of-freedom motion base, and a multi-channel data acquisition system. Computerized flight performance data (e.g., headings, altitudes, airspeeds, turn rates, etc.) were collected and stored on a Digital Equipment Corporation (Nashua, NH) VAX 11/780.

UH-60 Aircraft. All aircraft flights (performed in one of the four Dexedrine studies) were conducted in a specially-instrumented UH-60 helicopter (Sikorsky Aircraft, Stratford, CT) equipped with a locally-constructed, computerized flight monitoring system referred to as the Aeromedical Instrumentation System (AIS). This system recorded the same aspects of pilot performance that were collected in the simulator studies, and, at the conclusion of each flight, the data were downloaded to the Laboratory's main computer. The final analysis of all flight data, regardless of whether they were collected from the simulator or the aircraft, used the same scoring algorithms.

Waking Electroencephalographic (EEG) Evaluations. EEGs were recorded via Grass (Quincy, MA) E5SH electrodes (filled with SigmaGel electrolyte) from electrode site C<sub>Z</sub>. Data were amplified and stored on a Cadwell Spectrum 32 (Kennewick, WA). The low and high filters were set at 0.53 and 20 Hz, respectively, and the 60 Hz notch filter was used.

Profile of Mood States (POMS). Mood was assessed with the vigor scale from the POMS (McNair, Lorr, and Droppleman, 1981), a 65-item test which measures affect on six scales: 1) tension-anxiety, 2) depression-dejection, 3) anger-hostility, 4) vigor-activity, 5) fatigue-inertia, and 6) confusion-bewilderment.

## Procedure

Overview. The overview here is based on the schedule used for the 40-hour continuous-wakefulness studies. Note that there was an extra sleep-deprivation day (excluded from the

present data analysis) and one extra recovery day (between the deprivation periods) in the 64-hour Dexedrine study. Volunteers arrived at the Laboratory on Sunday for prescreening and preparation. Training sessions were conducted at 0900, 1300, and 1700 on Monday (training day) following the administration of a 2.5 mg test dose of Dexedrine (in the case of the Dexedrine studies). On Tuesday (control) and Thursday (control), there were testing sessions at these times as well. On Wednesday (the deprivation day in the first cycle), and on Friday (the deprivation day in the second cycle), testing sessions occurred at 0100, 0500, 0900, 1300, and 1700. On these days, drug or placebo doses were administered at 0000, 0400, and 0800 in the Dexedrine studies and at 2300, 0300, and 0700 in the modafinil study. At each dose time, subjects received either the stimulant or matching placebo. Either placebo or stimulant was administered every dose time within a specific deprivation cycle (e.g., subjects either received stimulant three times consecutively or placebo three times consecutively). The study was double blind and counterbalanced, and subjects were randomly assigned to a specific drug/placebo order upon arrival.

Schedule. The general schedule is shown in Table 1 (but counterbalancing was used in the studies). Note that there were two deprivation cycles separated by an 8-hour recovery sleep for each of the volunteers. The deprivation cycles began at 0700 on the morning of one day and ended at 2300 on the night of the following day. Each deprivation cycle included eight testing sessions at the times noted above. Each session began with a 1-hour flight, continued with the EEG (approximately 20 minutes after the flight), and concluded with the POMS (approximately 1 hour and 20 minutes after each flight). There were other tests conducted as well; however, these will not be presented here because the same tests were not administered across all five studies.

**Table 1. Schedule for Each of the Five Studies.**

<i>Time</i>	<i>Monday</i>	<i>Tuesday</i>	<i>Wednesday</i>	<i>Thursday</i>	<i>Friday</i>	<i>Saturday</i>	<i>Sunday</i>
0000		Sleep	Sleep	<b>DRUG</b>	Sleep	<b>PBO</b>	Sleep
		^	^	Simulator	^	Simulator	^
		^	^	EEG	^	EEG	^
		^	^	---	^	---	^
		^	^	POMS	^	POMS	^
0400		^	^	<b>DRUG</b>	^	<b>PBO</b>	^
		^	^	Simulator	^	Simulator	^
		^	^	EEG	^	EEG	^
		^	^	---	^	---	^
		^	^	POMS	^	POMS	^
0800		Wakeup	Wakeup	<b>DRUG</b>	Wakeup	<b>PBO</b>	Wakeup
		Training	Simulator	Simulator	Simulator	Simulator	
			EEG	EEG	EEG	EEG	Electrode
			---	---	---	---	removal
			POMS	POMS	POMS	POMS	
1200		Training	Simulator	Simulator	Simulator	Simulator	
			EEG	EEG	EEG	EEG	
			---	---	---	---	
			POMS	POMS	POMS	POMS	
1600	Start	Training	Simulator	Simulator	Simulator	Simulator	
	EEG		EEG	EEG	EEG	EEG	
	hookup		---	---	---	---	
			POMS	POMS	POMS	POMS	
2300		Bedtime		Bedtime		Bedtime	

Note: DRUG= 10 mg Dexedrine or 200 mg modafinil. PBO= matching placebo. Drug and placebo were counterbalanced between subjects. In the Modafinil study dose times were 1 hour earlier than shown above. POMS= Profile of Mood States. EEG= Eyes-open/eyes-closed electroencephalography.



Flight Performance. Regardless of whether subjects participated in one of the simulator studies or the in-flight study, the core maneuvers in the flight profiles were virtually identical. There were several maneuvers of the type typically flown in a UH-60 helicopter (and described further in the data analysis section). Some of these were flown with the automatic trim system engaged (the normal mode in the UH-60), while others were flown with the trim system off (to increase pilot workload). The automatic flight control system trim stabilizes the handling qualities of the simulator or aircraft. During each maneuver, subjects were required to maintain an airspeed of 120 knots, but specific targets for heading and altitudes changed from maneuver to maneuver. Subjects were instructed to make all turns at a standard rate of 3 degrees per second (or 15 degrees of roll angle) and to perform climbs and descents at a standard rate of 500 feet per minute.

Each 1-hour flight was coordinated by a safety pilot (or a pilot/console operator in the simulator) who instructed the subjects through the maneuvers. These individuals ensured that the subjects were flying correct headings, altitudes, airspeeds, etc., prior to initiating the scoring of each maneuver to minimize problems with large offset errors attributable to improper set up. Safety pilots and console operators refrained from providing feedback about performance during flights. In the few instances where the subjects fell asleep or became drowsy to the point of total inattention during the execution of a flight maneuver, the volunteer would be awakened at the conclusion of the maneuver's allotted time or when a determination was made that the maneuver would not be completed without intervention.

Based on the data collected between each maneuver's start and stop points, scores ranging from 0-100 (with 100 reflecting near perfect accuracy) were calculated for a variety of measures. These scores, based upon the extent to which subjects deviated from ideal

target values, expressed how well subjects maintained headings, altitudes, airspeeds, and other parameters. The scoring bands for each parameter are listed in Table 2. Individual parameter scores were averaged to produce one composite flight score for each iteration of each maneuver. This strategy avoided the necessity of performing analyses on multiple measures from each maneuver which would have been required if root mean square errors or some other type of deviation metric had been used. The reason is that while performance scores (all normalized to a scale from 0-100) can be averaged, there is no straightforward method for making composite deviation scores for airspeed (expressed in knots), heading (expressed in degrees), altitude (expressed in feet), and other parameters because each is represented in different units.

**Table 2. Scoring Bands for Flight Performance Data.**

Maximum deviation for scores of:

Measure (units)	100.0	80.0	60.0	40.0	20.0	0
Heading (degrees)	1.0	2.0	4.0	8.0	16.0	>16.0
Altitude (feet)	8.8	17.5	35.0	70.0	140.0	>140.0
Airspeed (knots)	1.3	2.5	5.0	10.0	20.0	>20.0
Slip (ball width)	0.0	0.1	0.2	0.4	0.8	>0.8
Roll (degrees)	0.8	1.5	3.0	6.0	12.0	>12.0
Vertical Speed (feet/m)	10.0	20.0	40.0	80.0	160.0	160.0
Turn Rate (degree/s)	0.3	0.5	1.0	2.0	4.0	>4.0

**EEG Evaluations.** EEG sessions occurred shortly after the flights. In each session, data were collected under eyes open and eyes closed conditions, for 1.5-2.0 minutes per condition. Data were recorded from F<sub>z</sub>, C<sub>z</sub>, and P<sub>z</sub>, referenced to linked mastoids (impedances were

5,000 ohms or less), but only the C<sub>z</sub> data will be reported here because the results from the other electrodes were found to be redundant. For scoring the data, each EEG record was visually scanned for three relatively artifact-free 2.5-second epochs (per eyes-open and eyes-closed iteration). The epoch lengths were based on software-driven requirements. Based on these EEG epochs, absolute power values expressed in millivolts squared were calculated (via Fast Fourier Transformations) for each of four frequency bands: delta (1.0-3.5Hz), theta (3.5-8.0 Hz), alpha (8.0-13.0 Hz) and beta (13.0-20.0 Hz). However, since theta activity is the most uniformly accepted EEG indication of significant fatigue from sleep deprivation, it will be the only EEG data included in the combined analysis reported here.

POMS. The POMS was given approximately one hour after the EEG. Subjects indicated on a standardized form how well each of 65 mood adjectives described the way he/she was presently feeling. Vigor scores were derived via either computerized scoring or hand scoring.

Data Analysis. All of the data were analyzed with BMDP4V, repeated measures analysis of variance (ANOVA). The basic design for the flight, EEG, and POMS data was a mixed-factorial ANOVA with one grouping factor (study) and two within-subjects factors (drug and session). The study factor had five levels (the 40-hour dextroamphetamine simulator study with males, the 40-hour dextroamphetamine simulator study with females, the 40-hour in-flight dextroamphetamine study, the 64-hour dextroamphetamine simulator study, and the 40-hour modafinil simulator study). Only the first part of the deprivation cycle from the 64-hour study was included in the present analysis since the 40-hour studies did not include a second deprivation day. The drug factor had two levels (stimulant versus placebo), and the session factor consisted of a minimum of eight levels (three baseline

sessions and five deprivation sessions). There were two additional levels of the session factor for the POMS vigor scores because the POMS was administered more frequently than the other evaluations.

For the flight performance data, there was an additional factor in the ANOVA which permitted the inclusion of the various basic types of maneuvers that were flown. Thus, the flight data were analyzed with a 4-way ANOVA (study-by-drug-by-session-by-maneuver). Of the total flight maneuvers, four were straight-and-levels (SLs), two were left standard-rate turns (LSRTs), three were right standard-rate turns (RSRTs), two were climbs, two were descents (except in the 64-hour Dexedrine study and the 40-hour modafinil study, where there were three descents), and one was a left-descending turn (LDT). An average was calculated for each type of maneuver, and this resulted in six levels of the maneuver factor (one for each type).

For all of the collected data, significant interactions among the various factors were pursued using analysis of simple effects and (when necessary) post-hoc, F-test comparisons. All data were checked for violations of the compound symmetry assumption, and where these were found, Huynh-Feldt adjusted degrees of freedom were applied.

## RESULTS

Flight performance, EEG, and POMS data were analyzed in three separate mixed-factorial analyses of variance. An overall depiction of the combined data is presented in figure 1.

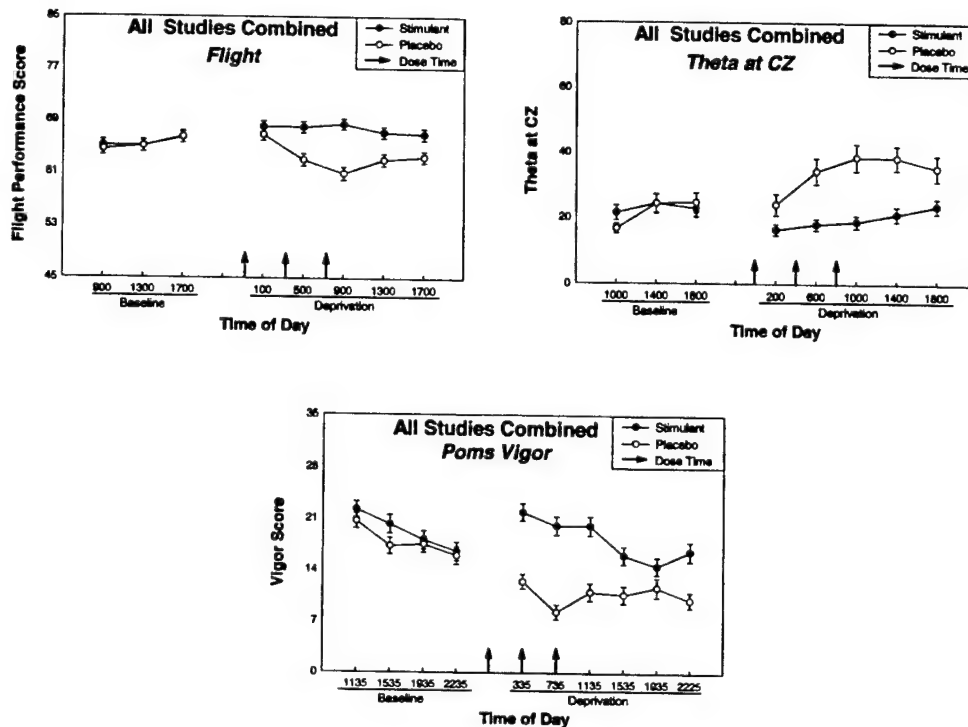


Figure 1. A summary of the flight performance, EEG, and POMS data from all studies.

### Flight Performance

Flight performance scores from the five studies were analyzed for differences under condition (placebo versus stimulant) across the three baseline flights (at 0900, 1300, and 1700) and five deprivation flights (0100, 0500, 0900, 1300 and 1700) within each of the six types of maneuvers (SL, LSRT, RSRT, Climb, Descent, and LDT). A 4-way ANOVA for study, condition, session, and maneuver was performed. Only drug-related (condition-related) main effects and interactions are presented here for the sake of brevity. Also, the primary objective of the present report is to establish the efficacy of the stimulants versus

placebo rather than to explore changes in performance which occurred as a result of other factors. Differences attributable only to the varied testing times or to whether subjects were tested in the simulator or the aircraft presumably hold little interest for the reader, and interpretations of these effects are often clouded by the presence of concurrent drug effects; however, it should be noted that the overall performance in the modafinil group did not differ systematically from performance in the dextroamphetamine groups.

There was a study-by-condition-by-session interaction on overall flight performance across the six maneuvers ( $F(21.5,155.9)=1.72, p=.0313$ ). Analysis of simple effects demonstrated this was due to a smaller effect size in the 40-hour in-flight dextroamphetamine study ( $p=.0554$ ) in comparison to the remaining four studies. However, as can be seen in figure 2, the differences between the stimulant and placebo conditions in the in-flight study were nonetheless similar to what was observed in the other studies. The fact that the stimulants exerted such reliable effects on performance was reiterated by the presence of an overall condition-by-session interaction ( $F(5.38,155.9)=20.27, p<.0001$ ). Analysis of simple effects indicated that the combined stimulant effect produced superior performance relative to placebo at all five of the sleep-deprivation sessions ( $p<.05$ ) while no differences occurred during the baseline (see figure 1, top left). Not surprisingly, there also was a main effect on the condition factor ( $F(1,29)=24.50, p<.0001$ ). This was due to an overall mean performance score of 63.4 under the stimulant condition in comparison to a score of 61.8 under the placebo condition (note that the baseline phase was included in this overall mean, making the stimulant effect appear smaller than it actually was).

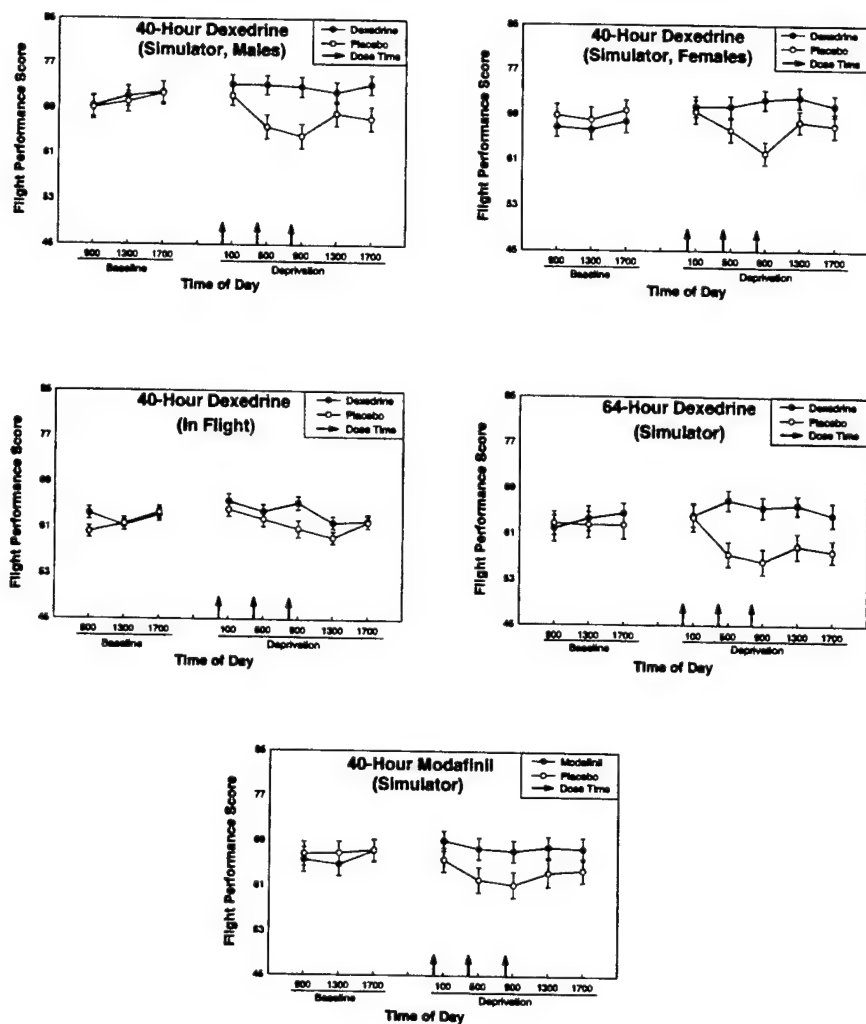


Figure 2. A depiction of the condition-by-session interaction on overall flight performance scores showing the consistency of effects across all five studies (note the slightly smaller drug effect in the in-flight investigation).

### EEG Data

Absolute power in the theta band from the eyes-open/eyes-closed EEG were analyzed with ANOVAs consisting of four factors: study (four simulator and one in-flight investigation), drug (placebo versus stimulant), session (1020, 1420, and 1820 on baseline; and 0220, 0620, 1020, 1420, and 1820 on the deprivation day), and eyes (eyes open/eyes closed). Again, for the sake of brevity, only the drug-related (condition-related) effects are presented. Also, since previous results from the five original studies, as well as from

investigations conducted by others, have shown theta to be the most sensitive EEG parameter to the effects of fatigue and sleep loss, it will be the only type of EEG activity presented.

The analysis of theta (3-8 Hz) activity demonstrated no differences across the five studies, indicating reliable stimulant-versus-placebo effects in each case (see figure 3). There was a condition-by-session interaction ( $F(7,196)=8.42, p<.0001$ ) and a condition main effect ( $F(1,28)=29.72, p<.0001$ ) across all of the studies collapsed. Analysis of simple effects revealed the interaction was attributable to significant attenuation of theta activity at each of the sleep-deprivation sessions under the stimulant relative to the placebo condition ( $p<.05$ ). During the baseline, there were no differences with the exception of an unexplained divergence at the first session (in which theta activity was greater during the stimulant baseline than during the placebo baseline). These effects are depicted in figure 3 (top right). While such an occurrence is difficult to explain, its presence actually makes the post-drug differences more impressive since the stimulants not only attenuated the impact of sleep loss, but also potentially reversed a preexisting fatigue state.

The overall condition main effect (with all other factors collapsed) was due to the presence of less theta activity under the stimulants than under placebo ( $20.8 \text{ mV}^2$  versus  $29.5 \text{ mV}^2$ ). As was the case with the flight data, this difference shows the positive effects of the drugs, but underestimates the overall stimulant effect because the baseline sessions and the deprivation sessions were averaged together.



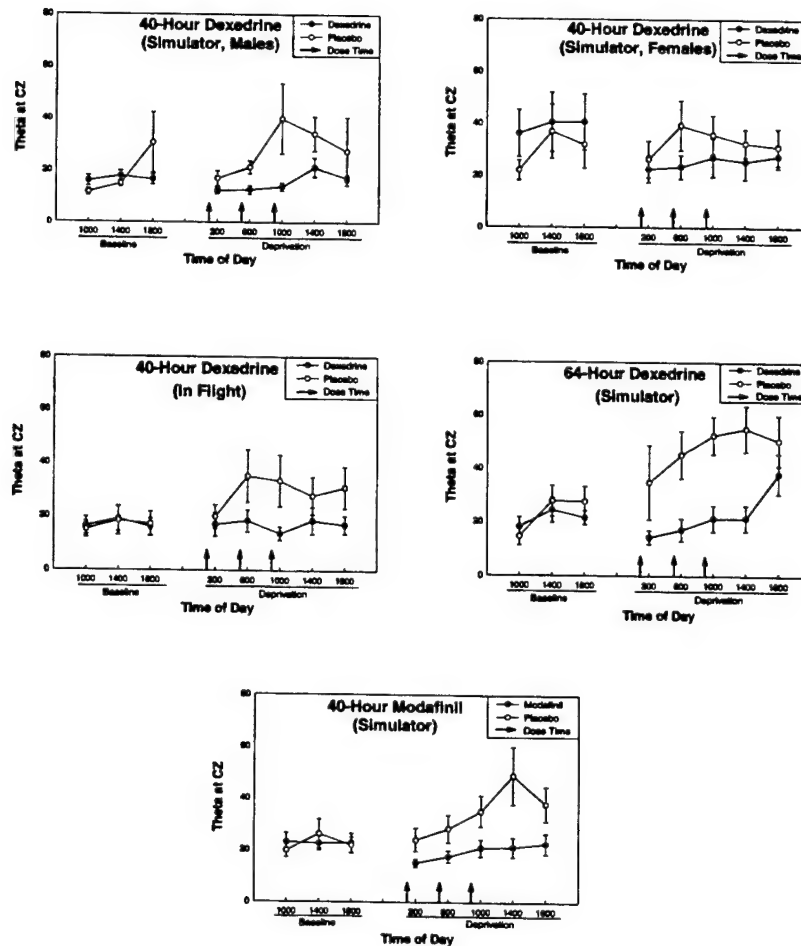


Figure 3. A depiction of the condition-by-session interaction for theta activity for each of the individual studies (there were no study-related differences in the magnitude of these effects).

### POMS Data

POMS vigor/activity scores under placebo and the stimulants at four baseline times (1120, 1520, 1920, and 2340) and six deprivation times (0320, 0720, 1120, 1520, 1920, and 2230) from all four studies were analyzed with an ANOVA for study, drug, and time (or session). Rather than conducting separate analyses on each of the six mood scales, the vigor/activity score was selected since it reflects subjective impressions of overall energy levels.

Analyses of these scores indicated there were no overall differences in the size of the stimulant/placebo effects across the five studies (see figure 4). However, there was a significant condition-by-session interaction ( $F(6.36,184.38)=21.21, p<.0001$ ) which was due to greater scores under the stimulant condition than the placebo condition at each of the deprivation sessions, whereas no differences occurred during the baseline (see figure 1, bottom). In addition, there was a condition main effect ( $F(1,29)=41.94, p<.0001$ ) consistent with the interaction observed earlier. Overall, vigor/activity scores were greater under the stimulant condition than under the placebo condition (18.33 versus 13.53, respectively).

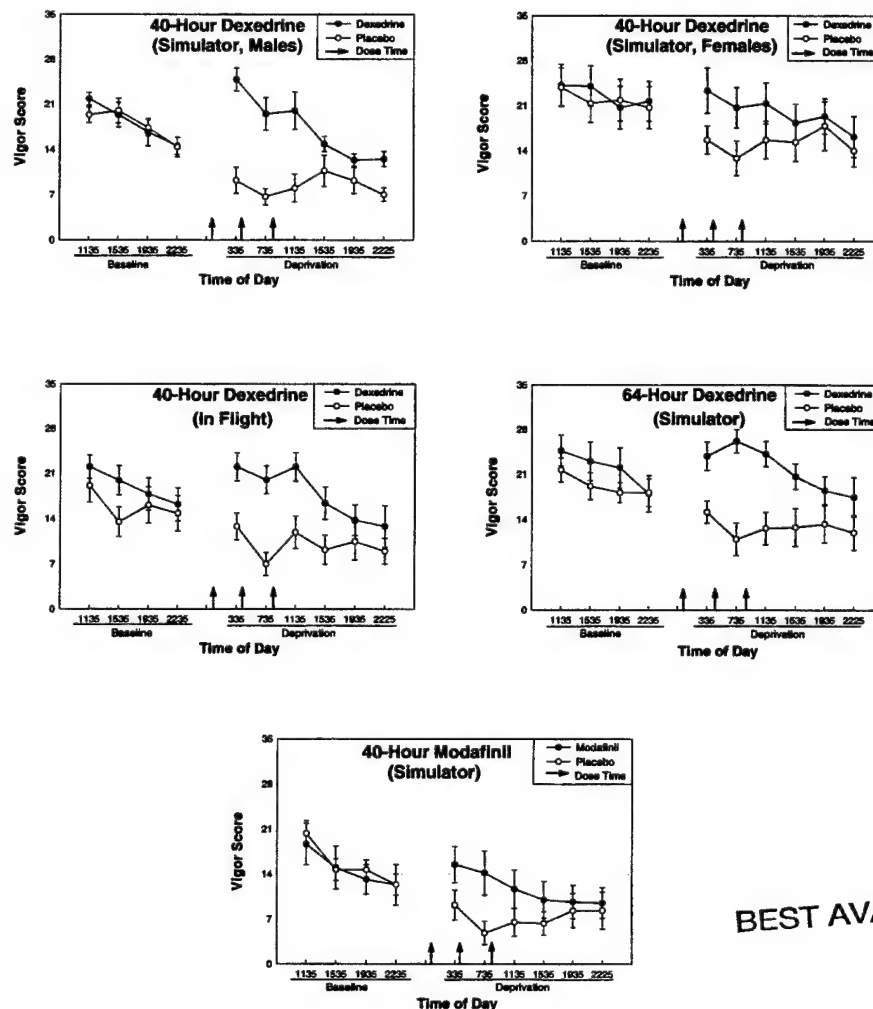


Figure 4. A depiction of the condition-by-session interaction for POMS vigor/activity scores for each of the individual studies (there were no study-related differences in the magnitude of these effects).

## DISCUSSION

This composite analysis of data from five previously-conducted stimulant studies supported and extended earlier conclusions that both dextroamphetamine and modafinil are useful for the short-term management of fatigue in sleep-deprived aviators. Both stimulants were particularly helpful after 20 to 29 hours without sleep (between 0300 and 1200), but beyond this time as well. While each of the individual studies from which the data sets were derived (four dextroamphetamine studies and one modafinil study) involved the testing of only small groups of volunteers (usually less than 10), the results were reliable across investigations.

The only instance of a difference in the magnitude of drug-by-session effects across studies was related to flight performance in the simulator versus the aircraft environment. Although the stimulant condition was associated with sustained performance throughout all of the assessments, actual in-flight testing was less sensitive to the positive impact of the drug (and the negative impact of sleep loss) compared to simulator testing. As has been discussed elsewhere (Caldwell and Roberts, 2000), this probably resulted from increased physiological activation in the aircraft versus the simulator (since the consequences of a mistake are more serious in the in-flight environment). Such an arousal increase tends to preserve performance under the placebo condition, resulting in smaller differences between the placebo and stimulant conditions.

Despite this effect, the flight data overall showed substantial performance declines under placebo at all five deprivation sessions, while performance under the stimulants did not. This finding, with short-interval 10-mg doses of dextroamphetamine and 200-mg doses of modafinil, extends those of Pigeau et al. (1995) who reported that widely spaced 20-mg

doses of dextroamphetamine and 300-mg doses of modafinil were effective for attenuating initial performance declines and for recovering already-degraded performance. In the present study, performance under the placebo condition declined sharply (particularly after 0100), reaching its lowest point by 0900, before recovering partially later in the day. Under the stimulant condition, flight skills remained at or above normal throughout the sleep deprivation.

The EEG data revealed that central-nervous-system activation was affected similarly in that Dexedrine and modafinil preserved EEG activity at more normal levels compared to placebo. Generally speaking, sleepiness and fatigue are known to accentuate the amount of slow-wave brain activity (Pigeau, Heslegrave, and Angus, 1987), and increased theta activity has been associated with generalized performance decrements on cognitive tasks (Belyavin and Wright, 1987). Thus, the stimulant-related attenuation of theta activity during sleep deprivation coincides well with the flight-performance results.

Subjective reports of vigor demonstrated that the stimulant condition also was associated with a perceived sustainment of energy levels compared to placebo. While there were sleepiness-related overall reductions in vigor scores under both drug and placebo, the effect was attenuated by the stimulants.

#### Evidence Supporting the Use of Stimulants

Taken together, the flight, EEG, and mood data in this investigation clearly support the contention that both dextroamphetamine and modafinil are effective fatigue countermeasures for sleep-deprived aviators. In addition, the uniformity of effects across the four dextroamphetamine studies demonstrates that this compound's ability to sustain alertness is

quite reliable. Subsequent testing with modafinil may produce a similar result, but at present, only one controlled aviation-specific investigation has been conducted with this medication. Because of the positive effects of both compounds, it seems logical that they should be considered a viable short-term remedy to the sweeping deleterious effects of fatigue that will invariably result from sleep restriction or total sleep deprivation. Although there are potential drawbacks associated with this pharmacological approach, the problems attributable to untreated fatigue seem more immediate and severe. For instance, numerous military mishaps have been attributed to fatigue, but none have thus far been attributed to stimulants despite the fact that these compounds have been used by military aviators during several conflicts (Cornum, Caldwell, and Cornum, 1997). Because of this and the fact that laboratory and field research have demonstrated the efficacy of stimulants as a viable fatigue countermeasure, the use of these compounds in limited situations should be considered. This is particularly true in military aviation where 1) there often is no choice except to fly the mission regardless of how tired the crew may be, and 2) the consequences of falling asleep at the controls are disastrous not only for the flight crew, but for the overall mission as well. Although military pilots can decline to accept flight missions due to concerns that fatigue may adversely affect their own safety and that of the crew, they would do so with the knowledge that their failure to take a short-term risk may indirectly compromise the safety of the people they are sworn to defend. In this situation, the aviator is under considerable pressure to accept the mission regardless of the known fatigue-related dangers, and the use of alertness-enhancing drugs certainly seems to be the best and the safest choice. In commercial aviation, the situation is complicated by the fact that 1) aircrew duty hours are more tightly restricted than is possible in the military setting (potentially making fatigue less

of a problem), and 2) the crew can decline to make a flight without compromising a mission that might imminently jeopardize the lives of innocent people and/or national security. Under these circumstances, the use of stimulants should be more carefully considered based on a straightforward cost/benefit analysis of the situation. However, in limited settings where a commercial aviator finds that fatigue has reached dangerous levels and a flight which is already underway might be adversely affected, it may be unwise to completely dismiss the possibility of using a stimulant for the short-term benefit. This is an issue that deserves consideration, especially in light of the development of newer ultra-long-haul jetliners and the shortage of qualified aviators. The problem of fatigue throughout the aviation system will only be compounded in the future.

#### Evidence Against the Use of Stimulants

Although pharmacological compounds are clearly capable of preserving the performance of fatigued aviators in the short term, there are other factors to consider. These must be carefully addressed before deciding to routinely rely on stimulant-based fatigue-management.

First, it is known that side effects may be a problem with some compounds. With regard to modafinil, Caldwell (2000) noted that repeated 200-mg doses (the amount tested in the modafinil study reported in this paper) produced side effects of nausea and vertigo in several of the participants. It is possible that these problems were related to the high dose of the drug (600 mgs within 24 hours as opposed to the normally used 200-400 mgs) or to the fact that all testing was carried out in a simulator (raising the possible confound of simulator sickness). However, this issue needs to be resolved before modafinil can be routinely used in the aviation environment. With regard to dextroamphetamine, it is well known that

amphetamine compounds are associated with substantial blood pressure increases, occasional increases in heart rate, possible euphoric psychological states, and idiosyncratic "over stimulation" that may manifest itself as manic behavior. The fact that such responses are unpredictable from individual to individual indicates that medical screening, to include preflight test dosing, is necessary to minimize the possibility of an unexpected adverse reaction in flight.

Second, there is the concern that physiological/psychological dependence may develop with an over-reliance on stimulants. While research with modafinil suggests little potential for dependence or abuse (Lyons and French, 1991), the same is not true of dextroamphetamine (Hoffman and Lefkowitz, 1990). However, Cornum, Caldwell, and Cornum (1997) suggest there is little evidence that occasional controlled use of stimulants (i.e., amphetamines) produces dependence in military aviators. Still, it is clear that indiscriminant, daily reliance on these compounds may create dependence and other problems. In addition, frequent use of stimulants will increase tolerance to the positive effects, systematically increasing the amount of medication required to overcome fatigue.

Third, there is the concern that stimulants will be used improperly as a substitute for sleep rather than as a short-term remedy for unavoidable sleep deprivation. The enthusiasm of most military and civilian aviators towards the mission may tempt them to opt for a stimulant in order to continue flying rather than obtaining the sleep which would allow alertness to recover naturally. Careful scheduling of duty, proper control over access to stimulants, and education about the importance of adequate restful sleep for proper fatigue management should prevent this substitution of stimulants for sleep. Thus far, no drug has been synthesized that is capable of replacing the need for sleep.

## SUMMARY AND CONCLUSIONS

Dexedrine has for years been proven effective for maintaining the performance of fatigued but otherwise normal personnel (Weiss and Laties, 1967) and modafinil is gaining acceptance as a possible dextroamphetamine alternative (Lyons and French, 1991; Pigeau et al., 1995). This is despite the fact that neither compound has been approved for this specific purpose by the U.S. Food and Drug Administration. Although it is true that long-term, indiscriminate administration of these or any other alertness-enhancing substances may pose both physical and psychological risks, there is no indication that aviators will abuse such compounds under controlled circumstances. In light of this fact, and in light of the present data which demonstrate the efficacy of these compounds for sustaining the alertness and performance of sleep-deprived pilots, it appears that well-controlled administration of dextroamphetamine, and possibly modafinil\*, should be considered appropriate for the short-term management of fatigue in select situations. However, it must be reemphasized that no stimulant can replace effective crew-rest scheduling or provide a substitute for restful, restorative sleep

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\* Approval for the use of modafinil for aviators must await further testing to rule out potential side effects. However, the efficacy of the drug has been demonstrated, and a recently-completed, but as yet unpublished, U.S. Air Force study in which the dosage was within the approved 400-mg range (as opposed to the 600 mg range used by Caldwell et al, (2000)) failed to detect vestibular effects (indicating that vertigo and nausea should not be a problem with the lower doses).



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